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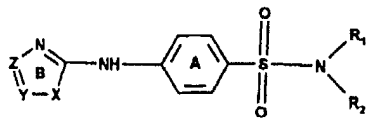

(I)

(57) Abstract

The invention relates to a compound of formula (I) wherein x is S or NH, and Y and Z are each CH; or X is NH and one of variables Y and Z is N and the other is CH; R_1 and R_2, independently of one another, represent hydrogen, C_1–C_7alkyl or C_1–C_7alkyl substituted by hydroxy, halogen, C_1–C_7alkoxy, carboxy, C_1–C_7alkoxycarbonyl, carbamoyl, C_1–C_7alkylcarbamoyl, di–C_1–C_7alkylcarbamoyl, C_3–C_8cycloalkyl or by C_3–C_8cycloalkyl which is substituted by C_1–C_7alkoxy–carbonyl, or represent C_2–C_7 alkanoyl; whereas at least one of variables R_1 and R_2 is different from hydrogen; or the group NR_1R_2 is linear C_2–C_6alkyleneamino that is unsubstituted or substituted. The ring A, apart from being substituted by $–SO_2NR_1R_2$ and –NH–, is unsubstituted or substituted one or more times; the ring B is substituted once or twice via a carbon atom of ring B or a salt thereof, especially a pharamaceutically acceptable salt thereof; to processes for their preparation, to pharmaceutical compositions and to the use of the compounds of formula (I) and their salts.

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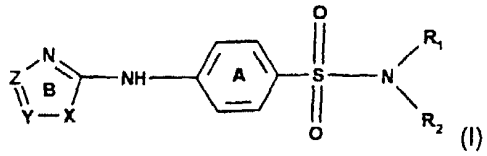
SUBSTITUTED BENZENESULFONAMIDE.DERIVATIVES AND THEIR PHARMACEUTICAL USE

The invention relates to a compound of formula (I)



(I)

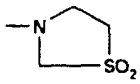
wherein

X is S or NH, and Y and Z are each CH; or

X is NH and one of variables Y and Z is N and the other is CH;

R_1 and R_2, independently of one another, represent hydrogen, C_1-C_7alkyl or C_1-C_7alkyl substituted by hydroxy, halogen, C_1-C_7alkoxy, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, C_3-C_8cycloalkyl or by C_3-C_8cycloalkyl which is substituted by C_1-C_7alkoxy-carbonyl, or represent C_2-C_7-alkanoyl;

whereas at least one of variables R_1 and R_2 is different from hydrogen; or

the group NR_1R_2 is linear C_2-C_6alkyleneamino that is unsubstituted or substituted by C_1-C_7alkyl, hydroxy-C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkoxy-C_1-C_7alkyl, C_1-C_7alkylthio-C_1-C_7alkyl, C_1-C_7alkanesulfinyl-C_1-C_7alkyl, C_1-C_7alkanesulfonyl-C_1-C_7alkyl, amino-C_1-C_7alkyl, C_1-C_7alkylamino-C_1-C_7alkyl, di-C_1-C_7alkylamino-C_1-C_7alkyl, hydroxy, cyano, amino, C_1-C_7alkylamino, di-C_1-C_7alkylamino, C_1-C_7alkanoyl, C_2-C_7hydroxylimino-alkyl, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, or by oxo, or is morpholino, thiomorpholino, 4-C_1-C_7alkylpiperazino, 4-pyridyl-piperazino, tetrahydroquinolin-1-yl, tetrahydroisoquinolin-2-yl, dihydroindol-1-yl or C_1-C_7alkoxycarbonyl-substituted dihydroindol-1-yl or is a group of formula 

; and

wherein

the ring A, apart from being substituted by $-SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, hydroxy, halogen and CF_3; and wherein the ring B is substituted once or twice via a carbon atom of ring B by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, and phenyl,

pyrroyl, furyl, thienyl and pyridyl, each unsubstituted or substituted one or more times by a substituent selected from the group consisting of hydroxy, halogen, C_1-C_7alkyl, halo-C_1-C_7alkyl, C_1-C_7alkoxy, halo-C_1-C_7alkoxy, C_2-C_7alkanoyloxy, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, amino, C_1-C_7alkylamino, di-C_1-C_7alkylamino and N-C_1-C_7alkanoyl-N-C_1-C_7alkylamino, or di-substituted by C_1-C_4alkylene-oxy-C_1-C_4alkylene;
or a salt thereof, especially a pharmaceutically acceptable salt thereof; to processes for their preparation, to pharmaceutical compositions and to the use of the compounds of formula (I) and their salts.

The compounds of formula (I) may be present in the form of salts, especially in the form of pharmaceutically acceptable salts. Acid addition salts may be formed with the basic amino group. As acid component there come into consideration, for example, strong inorganic acids, such as mineral acids, for example hydrohalic acids, e.g. hydrochloric acid, or strong organic carboxylic acids, e.g. acetic acid or trifluoroacetic acid, or organic sulfonic acids, e.g. methanesulfonic acid or p-toluenesulfonic acid. Also included are salts that are not suitable for therapeutic use, which can be used, for example, in the isolation and purification of free compounds of formula (I) or their pharmaceutically acceptable salts. Only the pharmaceutically acceptable, non-toxic salts are used therapeutically and they are therefore preferred.

Where they contain at least two optically active carbon atoms the compounds according to the invention may accordingly be in the form of stereoisomers, mixtures of stereoisomers or in the form of the (substantially) pure diastereoisomers. Corresponding compounds having one optically active carbon atom are in the form of racemates, especially in the form of (substantially pure) enantiomers. Corresponding stereoisomers are likewise covered by the present invention.

Unless defined to the contrary, the general terms used hereinabove and hereinbelow have the following meanings.

C_1-C_7Alkyl is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl radical. Preference is given to C_1-C_4alkyl, especially methyl.

C_1-C_7Alkoxy is e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy or heptyloxy radical. C_1-C_4Alkoxy is preferred. Methoxy is especially preferred.

C_1-C_7Alkoxy-C_1-C_7alkyl is especially C_1-C_4alkoxy-C_1-C_4alkyl, such as methoxymethyl, methoxyethyl, 2-ethoxyethyl, 2-n-propyloxyethyl or ethoxymethyl. Methoxymethyl, ethoxymethyl and 1-methyl-2-methoxyethyl are preferred.

C_1-C_7Alkoxy-C_1-C_7alkoxy-C_1-C_7alkyl is especially C_1-C_4alkoxy-C_1-C_4alkoxy-C_1-C_4alkyl, such as methoxymethoxymethyl, ethoxymethoxymethyl, 2-methoxy ethoxymethyl, 2-ethoxy-2-ethoxy-methyl, 2-n-propyloxyethoxy-methyl or ethoxymethyl. 2-Methoxy-ethoxymethyl or 2-ethoxyethoxymethyl are preferred.

C_3-C_8Cycloalkyl is especially C_4-C_7cycloalkyl, such as cyclopropyl, cyclobutyl, cyclohexyl or cycloheptyl.

Carboxy-C_1-C_7alkyl is especially carboxy-C_1-C_4alkyl, such as carboxymethyl, 2-carboxyethyl or 3-carboxypropyl.

C_1-C_7Alkoxycarbonyl is especially C_1-C_4alkoxycarbonyl, such as methoxy-, ethoxy-, n-propyloxy- or n-butyloxy-carbonyl.

C_1-C_7Alkyl-carbamoyl is especially C_1-C_4-alkyl-carbamoyl, such as methyl-, ethyl-, n-propyl-, or n-butyl-carbamoyl.

Di-C_1-C_7alkyl-carbamoyl is especially di-C_1-C_4-alkyl-carbamoyl, such as dimethyl-, methyl-ethyl-, diethyl-, di-n-propyl-, or di-n-butyl-carbamoyl.

C_1-C_7Alkoxycarbonyl-C_1-C_7alkyl is especially C_1-C_4alkoxycarbonyl-C_1-C_4alkyl, such as methoxy-, ethoxy-, n-propyloxy- or n-butyloxy-carbonyl-methyl or -ethyl. Preferred examples are 1-methoxycarbonylethyl, 1-methoxycarbonyl-2-methylethyl and 1-methoxycarbonyl-2-methylpropyl.

Aminocarbonyl-C_1-C_7alkyl is especially aminocarbonyl-C_1-C_4alkyl, such as aminocarbonyl-methyl, -ethyl or -n-propyl.

C_1-C_7Alkylaminocarbonyl-C_1-C_7alkyl is especially C_1-C_4alkylaminocarbonyl-C_1-C_4alkyl, such as methyl-, ethyl- or n-propyl-aminocarbonylmethyl. A preferred example is 1-methyl amino-2-methylpropyl.

Di-C_1-C_7alkylaminocarbonyl-C_1-C_7alkyl is especially di-C_1-C_4alkylaminocarbonyl-C_1-C_5alkyl, such as dimethyl-, diethyl- or di-n-propyl-aminocarbonylmethyl.

Hydroxy-C_1-C_7alkyl is especially hydroxy-C_1-C_4alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl. A preferred example is hydroxymethyl.

C_2-C_6Alkyleneamino is cyclobutylene-, cyclopentylene- or cyclohexylene-amino (pyrrolidino, piperidino or azepino). Cyclobutylene- and cyclohexylene-amino are preferred.

C_1-C_7Alkylthio-C_1-C_7alkyl is especially C_1-C_4alkylthio-C_1-C_4alkyl, such as methylthiomethyl, 2-methylthio-ethyl, ethylthiomethyl or 2-ethylthio-ethyl.

C_1-C_7Alkanesulphinyl-C_1-C_7alkyl is especially C_1-C_4alkanesulphinyl-C_1-C_4alkyl, such as methanesulphinylmethyl, 2-methanesulphinyl-ethyl, ethanesulphinylmethyl or 2-ethanesulphinyl-ethyl.

C_1-C_7Alkanesulphonyl-C_1-C_7alkyl is especially C_1-C_4alkanesulphonyl-C_1-C_4alkyl, such as methanesulphonylmethyl, 2-methanesulphonyl-ethyl, ethanesulphonylmethyl or 2-ethanesulphonyl-ethyl.

Hydroxylimino-C_1-C_7-alkyl is especially hydroxylimino-C_1-C_4-alkyl, such as hydroxylimino-methyl.

Amino-C_1-C_7alkyl is especially amino-C_1-C_4alkyl, such as aminomethyl, 2-aminoethyl, 3-aminopropyl or 4- aminobutyl.

C_1-C_7Alkyl-amino-C_1-C_7alkyl is especially C_1-C_4alkyl-amino-C_1-C_4alkyl, such as methylaminomethyl, ethylaminomethyl or 2-ethylamino-ethyl.

Di-C_1-C_7alkyl-amino-C_1-C_7alkyl is especially di-C_1-C_4alkyl-amino-C_1-C_4alkyl, such as dimethylaminomethyl, diethylaminomethyl or 2-di-ethylamino-ethyl.

Pyrrolyl is especially 2- or 3- pyrrolyl.

Furyl is 2- or 3-furyl.

Thienyl is 2- or 3-thienyl.

Pyridyl is 2-, 3- or 4-pyridyl.

C_1-C_7Alkylamino is especially C_1-C_4alkylamino, such as methyl-, ethyl-, n-propyl-, isopropyl- or n-butyl-amino. Methylamino is preferred.

Di-C_1-C_7alkylamino is especially di-C_1-C_4alkylamino, such as dimethyl-, diethyl- or diisopropyl-amino.

C_1-C_7Alkoxy-C_1-C_7alkoxy is especially C_1-C_4alkoxy-C_1-C_4alkoxy, such as methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

C_1-C_7Alkanoyl is especially C_2-C_5alkanoyl, such as formyl, acetyl, propionyl or pivaloyl.

C_2-C_7Alkanoyloxy is especially C_2-C_5alkanoyloxy, such as acetyloxy, propionyloxy or pivaloyloxy.

Halogen is especially halogen having an atomic number of up to and including 35, that is to say fluorine, chlorine or bromine, and also includes iodine. Chlorine is preferred.

Halo-C_1-C_7alkyl is especially halo-C_1-C_4alkyl, such as fluoromethyl, fluoroethyl, chloromethyl, trifluoromethyl, trichloromethyl, chloroethyl or 1,1,1-difluorochloroethyl.

Halo-C_1-C_7alkoxy is especially halo-C_1-C_4alkoxy, such as fluoromethoxy, fluoroethoxy, chloromethoxy, trifluoromethoxy, trichloromethoxy, chloroethoxy or 1,1,1-difluorochloroethoxy.

C_1-C_4Alkyleneoxy-C_1-C_4alkylene is especially C_1-C_2-alkyleneoxy-C_1-C_2alkylene, such as methyleneoxymethylene.

(Hetero-)Aryl radicals, for example, ring A or corresponding radicals attached to ring B, may be substituted one or more times, e.g. twice or three times.

Preferred C_2-C_6alkyleneamino [-N(R_1)(R_2)] is pyrrolidino, piperidino or azepino. Preferred substituted C_2-C_6alkyleneamino is pyrrolidino which is especially mono-substituted. Preferred substituents of pyrrolidino are C_1-C_4alkoxy-C_1-C_4alkyl, especially methoxymethyl or ethoxymethyl, C_1-C_4alkanesulphonyl-C_1C_4alkyl, especially methanesulphonylmethyl, C_1-C_4alkyl, especially methyl, ethyl or propyl, hydroxy-C_1-C_4alkyl, especially hydroxymethyl, cyano, or C_1-C_4alkoxycarbonyl, especially methoxycarbonyl, all of which are preferably located in position 2, or is mono-substituted by C_1-C_4alkoxy, especially methoxy, which is preferably located in position 3, of the pyrrolidino ring.

Obesity is a widespread phenomenon that is responsible for a whole series of pathological symptoms and has an adverse effect on health generally. In addition, obesity is associated with considerable socio-economic costs and constitutes a serious financial burden on the healthcare system. In order to solve this problem it is necessary to find an approach with which obesity and its associated diseases and disorders can be treated systematically. It has surprisingly been found that eating behaviour can be regulated by modulation of the neuropeptide Y(NPY) receptor subtype Y5.

It has been shown in extensive pharmacological studies that the compounds (I) and their pharmaceutically acceptable salts are suitable as antagonists of the neuropeptide Y5 receptor subtype.

The compounds according to the present invention and their pharmaceutically acceptable salts have been shown to have a marked and selective affinity for the receptor subtype Y5

(demonstrated in Y5-binding studies) and exhibit antagonistic properties *in vitro* and *in vivo*. Those properties are manifested *in vitro* by the ability of the compounds to inhibit the NPY-induced increase in calcium in stably transfected cells that express the Y5 receptor. *In vivo* the antagonistic effect is manifested by the ability to inhibit in conscious rats the intake of food induced by intraventricular administration of NPY or by withdrawal of food for 24 hours.

Binding experiments

The selective affinity of the compounds (according to the present invention) for the Y5 receptor has been demonstrated in a Y5-binding assay on LM(tk-)-hY5-7 cel ls, which provide long-term expression of the human NPY5 receptor, and on HEK-293 cells, which provide long-term expression of the NPY5 receptor of rats.

The following buffers were used for the preparation of the membranes and for the binding assay:
a) buffer 1 (homogenisation buffer, pH 7.7 at 4°C) contains Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediaminetetraacetic acid (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) buffer 2 (suspension buffer, pH 7.4 at room temperature) contains N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim, Germany] (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM); c) buffer 3 (binding buffer, pH 7.4 at room temperature) contains HEPES (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

The cells are washed in phosphate-buffered saline solution and collected using a rubber blade. Homogenisation of the cells is carried out using a Polytron homogeniser (3 pulses of 8 seconds) in ice-cooled hypotonic buffer solution (buffer 1, pH 7.7 at 4°C). The homogenate is centrifuged for 20 minutes at 32 000 g and 4°C. The sediment is resuspended in the same buffer and again centrifuged. The resulting sediment is suspended in buffer 2. The protein concentration is determined using the Coomassie Blue method [Pierce, Socochim, Lausanne, CH]. Bovine serum albumin is used as standard. The crude membrane suspension is divided into aliquots, frozen in liquid nitrogen and stored at -80°C. Before use, 0.1% (1 mg/ml) bovine serum albumin is added.

^{125}I-[Pro^{34}]hPYY (60 pM final concentration, Anawa, Wangen, Switzerland], dissolved in buffer 3, is used as radioligand.

All compounds to be tested are dissolved in 10^{-2} M dimethyl sulfoxide (DMSO) and diluted to 10^{-3} M with buffer 3. Further dilutions are made with buffer 3 plus 10 % DMSO. Incubations are carried out in Millipore Multiscreen FB filter plates [Millipore, Bedford, USA]. The filters present in each sample well are pretreated with 2 % polyethyleneimine for 30 minutes and before use are rinsed once with 300 microl of buffer 3. The following substances are introduced by pipette into each sample well: 60 microl of buffer 3, 20 microl of ^{125}I-[Pro^{34}]hPYY (600 pM), 20 microl of test compound (or binding buffer plus 10 % DMSO for the controls), 100 microl of crude membrane suspension (about 10 microg of protein). Incubation is carried out at room temperature for two hours. Binding that is still present in the presence of 1 microM [Pro^{34}]hPYY [BACHEM, Bubendorf, Switzerland] is defined as non-specific binding. The incubation is terminated by rapid filtration and washing four times with 300 microl of phosphate-buffered saline solution. The filters are removed from the wells of the plate, inserted into plastics test tubes and examined for their radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC50 values of the compounds (according to the present invention) at the human Y5 receptor lie predominantly between about 0.1 nM and about 10 microM. For example, for representatives of the working examples following binding data (IC_{50}) have been determined:

example 1:	0.016 µmol/l	example 12:	0.002 µmol/l
example 17:	0.012 µmol/l	example 24:	0.013 µmol/l
example 77:	0.0068 µmol/l	example 81:	0.0032 µmol/l.

Measurement of the calcium increase

To determine the antagonistic properties of the compounds (according to the filed invention) *in vitro*, stably transfected LM(tk-)-hY5-7 cells are used in which an NPY-induced increase in calcium has been measured as follows: the cells are collected in a medium containing EDTA (0.5 mM) and phosphate-buffered saline solution (PBS). The cells are then washed in phosphate-buffered saline solution and incubated for 90 minutes at room temperature and pH 7.4 with 10 microM FLUO-AM (fluoro-3-acetoxymethyl ester supplemented by pluronic

acid, as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition: (NaCl 120 mM, $MgCl_2$ 1 mM, KCl 5.4 mM, NaH_4PO_4 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM, HEPES 10 mM, insulin 10 U/litre, BSA 0.1 %). After centrifugation, the cells are resuspended in the cell culture buffer in a concentration of 3 -4 million cells/ml, and 200 µM sulfinpyrazone are added.

The increase in calcium is measured at room temperature in a millititre plate using a Cytofluor 2350 (Millipore) at wavelengths of 485 nm (excitation) and 530 nm (emission). 180 microl of the cell suspension are incubated for 5 minutes in the presence of different amounts of the compounds, which have been dissolved in 2 microl of DMSO (each x 3) (or in 2 microl of DMSO for the controls). Then NPY is added in a final concentration of 100 nM. The concentrations of the compounds that result in 50% inhibition of the maximum increase in calcium are calculated.

In this cell system, an increase in calcium is induced by NPY at an EC50 of 50 nM. The data were evaluated using Microsoft Excel software. The concentrations resulting in 50% inhibition of the initial values of the controls are given as IC50 values. The IC50 values were determined for the compounds according to the present invention and their pharmaceutically acceptable salts.

The ability of the compounds and their pharmaceutically acceptable salts to inhibit the NPY-induced increase in intracellular calcium provides evidence of their antagonistic properties. The IC50 values lie predominantly between about 0.1 nM and about 10 microM.

Determination of NPY-induced food intake in conscious rats

Furthermore, this antagonism to the Y5 receptor subtype is also observed *in vivo* in conscious rats in which the NPY-induced intake of food can be inhibited. For those tests the food intake of satiated rats after cerebroventricular administration (i.c.v.) of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] with and without additional administration of the compounds (according to the present invention) was determined. All tests were carried out using male Sprague-Dawley rats weighing between 180 and 220 g. The animals were kept individually in Makrolon cages with a light/darkness rhythm of 11:13 hours (dark from 18.00) at controlled temperatures (21–23°C). Water and

food (NAFAG Lab-feed pellets) [NAFAG, Gossau, Switzerland] were available *ad libitum*. Under Vetanarcol anaesthesia (50 mg/kg, intraperitoneal) [VETERINARIA AB, Zürich, Switzerland] all rats were implanted with a stainless steel guide cannula towards the right ventricle of the brain. The stereotactic coordinates were: -0.8 mm anterior and +1.3 mm lateral of the bregma, the level being set at -2.0 mm below the interaural line. The guide cannula was positioned on the dura. The injection cannulae projected out of the guide cannulae -3.8 mm in the ventral direction (relative to the surface of the skull). Post-operatively the animals were allowed a recovery period of at least five days before they were used for the tests.

The position of the cannula was checked post-operatively two days before the actual tests by testing the feeding behaviour of all rats after a cerebroventricular (i.c.v.) injection of 300 pmol NPY. To determine NPY-induced food intake, only rats that had consumed at least 2 g of food within a period of 2 hours after the NPY injection were used. The injections were carried out in the morning, two hours after the start of the light phase. The peptides were administered in 5–10 µl of artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland]. ACSF contains NaCl 124mM, KCl 3.75mM, $CaCl_2$ 2.5mM, $MgSO_4$ 2.0mM, KH_4PO_4 0.22mM, $NaHCO_3$ 26mM and glucose 10mM. NPY (300 pmol) was administered cerebroventricularly 10 to 60 minutes after the administration of the com pounds or of the respective vehicle DMSO/water (10% v/v), Cremophor/water (20% v/v) [SIGMA, Buchs, Switzerland] or Tween 80/water (10% v/v) [FLUKA, Buchs, Switzerland].

The food intake was determined by placing a preweighed amount of feed pellets in the cages at the time of the NPY injection. At each of the time points indicated the pellets were removed from the cages and replaced by fresh preweighed pellets.

All results are given as mean values ± SEM. The statistical evaluation was made by variance analysis. *Post hoc* comparisons were made using the Student-Newman-Keuls test. Statistical significance was assumed at $p<0.05$.

Compounds according to the present invention, administered orally, intraperitoneally, subcutaneously, intravenously and transdermally, brought about an inhibition of NPY-induced food intake in rats, predominantly between about 0.01 and about 100 mg/kg.

Determination of food intake in rats after withdrawal of food for 24 hours

On the basis of the observation that withdrawal of food induces a rise in the NPY level in the hypothalamus, it is assumed that NPY is responsible for food intake induced by hunger. The compounds (according to the filed invention) were therefore also tested in rats after withdrawal of food for 24 hours. These tests were carried out with male Sprague-Dawley rats weighing between 180 and 250 g. The animals were kept in individual cages for the duration of the test and (with the exception of the withdrawal of food for 24 hours) received food and tap water *ad libitum*. The animals were kept at 22 ± 2°C and in controlled humidity with a light/darkness rhythm of 12:12 hours (light from 6.00 to 18.00). After being placed in the individual cages, the rats were given two weeks to become accustomed to their new environment and to the powdered food or feed pellets [NAFAG, Gossau, Switzerland] (acclimatisation phase). At the end of that phase, the animals were given no food for 24 hours (beginning 8.00 a.m.). At the end of the fasting phase, either the compounds according to the present invention or an equal volume of the respective vehicle DMSO/water (10%, v/v), Cremophor/water (20%, v/v) or Tween 80/water (10%, v/v) were administered to the animals intraperitoneally, intra venously or orally. 10 to 60 minutes later the animals were given food again. During the subsequent 24 hours, the food intake was measured at various time points. The inhibition of food intake brought about by the compounds according to the present invention was given as a percentage of the food intake of the control animals treated with the vehicle.

In this model, using rats from which food had been withdrawn, the compounds according to the present invention, administered orally, intraperitoneally, subcutaneously or intravenously, brought about an inhibition of food intake; the ED50 lay between 0.01 and about 100 mg/kg.

Determination of the food intake in obese Zucker rats

The anti-obesity activity of the compounds according to the present invention was also demonstrated in obese sugar rats, which are a known animal model for obesity. The studies were carried out using male obese Zucker rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. The animals were kept individually in metabolism cages for the duration of the study and received food in powder form and tap water *ad libitum*. The animals were kept in a room with a light/darkness rhythm of 12:12 hours (light from 8.00 to

20.00) at a temperature of 24°C and with controlled humidity. After being placed in the metabolism cages, the rats were given six days to become accustomed to their new environment and to the powdered food (acclimatisation phase). At the end of that phase, the food consumption during the light and darkness phases was determined. After a three-day control phase the animals were treated with the compounds according to the present invention or with the DMSO/water (10% v/v), Cremophor/water (20% v/v) [SIGMA, Buchs, Switzerland] or Tween 80/water(10% v/v) [FLUKA, Buchs, Switzerland].

The compounds according to the present invention, administered orally, intraperitoneally, subcutaneously or intravenously, brought about an inhibition of food intake in obese sugar rats, predominantly between about 0.01 and about 100 mg/kg.

Determination of food intake in obese mice

The anti-obesity activity of the compounds according to the present invention was also demonstrated in genetically obese mice. The tests were carried out using male and/or female mice having the ob/ob mutation (The Jackson Laboratory, Bar Harbor, ME) (C57BL/61-ob) weighing between 30 and 80 grams. The mice were kept individually in Makrolon or metabolism cages and received food in powder form and tap water *ad libitum*. The mice were kept at 24 °C and with a light/darkness rhythm of 12:12 hours (light from 8.00 to 20.00). After being placed in the cages, the mice were given six days to become accustomed to their new environment (acclimatisation phase). After a three-day control phase in which the food intake and body weight were monitored, the mice were treated with the compounds according to the filed invention or with the DMSO/water (10% v/v), Cremophor/water (20% v/v) [SIGMA, Buchs, Switzerland] or Tween 80/water (10% v/v) [FLUKA, Buchs, Switzerland].

The compounds according to the present invention, administered orally, intraperitoneally, subcutaneously or intravenously, brought about an inhibition of the food intake in obese ob/ob mice, predominantly in a range between about 0.01 and about 100 mg/kg.

The animal experimental tests described above clearly show that the Y5 receptor subtype is the primary mediator of NPY-induced food intake and that corresponding antagonists can

be used in the treatment of obesity and related disorders [*Nature, Vol. 382, 168 - 171 (1996)].*

The compounds according to the present invention are capable of inhibiting food intake induced either by cerebroventricular administration of NPY or by withdrawal of food as well as being capable of inhibiting the spontaneous intake of food in obese sugar rats and ob/ob mice. Accordingly, the compounds (according to the filed invention) act against the binding of the neuropeptide Y (NPY) to the Y5 receptor subtype (NPY-antagonism) and could be used especially in the treatment and prevention of disorders or diseases that are associated with the Y5 receptor subtype, that is to say in which the NPY Y5 receptor subtype is involved. They could especially be used in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidaemia and hypertonia. Furthermore, they could be used in the treatment of loss of memory, epileptic convulsions, migraine, sleep disorders and pain, and additionally in the treatment of sexual disorders, depression, anxiety states, cerebral haemorrhages, shock, decompensated cardiac insufficiency, nasal congestion and diarrhoea.

The invention relates to a method of treating diseases and disorders associated with the NPY Y5 receptor subtype, which could be used especially in the prophylaxis and treatment of disorders and diseases in which the NPY Y5 receptor subtype is involved, and especially in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidaemia and hypertonia. Furthermore, they could be used in the treatment of loss of memory, epileptic convulsions, migraine, sleep disorders and pain, and additionally in the treatment of sexual disorders, depression, anxiety states, cerebral haemorrhages, shock, decompensated cardiac insufficiency, nasal congestion and diarrhoea. The method comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt of such a compound, to warm-blooded animals, including human beings, that require such treatment.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt of such a compound, as has been described hereinabove and as will be described hereinbelow also for the preparation of a medicament for the prophylaxis and treatment of corresponding diseases or disorders.

The invention relates to a medicament comprising a compound of formula (I) or a pharmaceutically acceptable salt of such a compound, as has been described hereinabove and as will be described hereinbelow also for the treatment of corresponding diseases or disorders.

The invention relates especially to a compound of formula (I) wherein

X is S or NH, and Y and Z are each CH; or

X is NH and one of variables Y and Z is N and the other is CH;

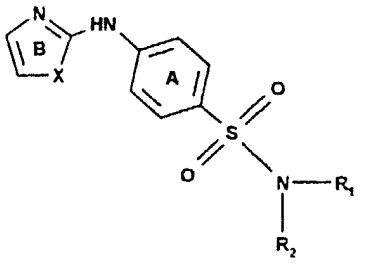
R_1 is C_1-C_7alkyl or C_1-C_7alkyl substituted by hydroxy, halogen, C_1-C_7alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, , C_3-C_8cycloalkyl or by C_3-C_8cycloalkyl which is substituted by C_1-C_7alkoxycarbonyl;

whereas at least one of variables R_1 and R_2 is different from hydrogen;

R_2 is hydrogen, C_1-C_7alkyl or hydroxy-C_1-C_7alkyl;

or a salt thereof, especially a pharmaceutically acceptable salt thereof.

The invention relates especially to a compound of formula (I')



(I')

wherein

R_1 is C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, carboxy-C_1-C_7alkyl, C_1-C_7alkoxycarbonyl-C_1-C_7alkyl, aminocarbonyl-C_1-C_7alkyl, C_1-C_7alkylaminocarbonyl-C_1-C_7alkyl or di-C_1-C_7alkylamino-carbonyl-C_1-C_7alkyl; and

R_2 is hydrogen or C_1-C_7alkyl; or

the group NR_1R_2 is C_4-C_6alkyleneamino that is unsubstituted or substituted by C_1-C_7alkoxy, hydroxy-C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl or by C_1-C_7alkoxycarbonyl, or is morpholino, thiomorpholino or C_1-C_7alkoxycarbonyl-substituted 2,3-dihydro-indol-1-yl;

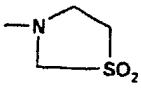
X is -S- or -NH-; and wherein

the ring A, apart from being substituted by -$SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, hydroxy, halogen and CF_3; and wherein

the ring B is substituted once or twice by a substituent selected from the group consisting of C_1-C_7alkyl, furyl and pyridyl, and phenyl that is unsubstituted or substituted one or more times by a substituent selected from the group consisting of halogen, C_1-C_7alkoxy, amino, C_1-C_7alkylamino and di-C_1-C_7alkylamino; or a salt thereof.

The invention relates especially to a compound of formula (I') wherein
R_1 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkyl-aminocarbonyl-C_1-C_4alkyl; and
R_2 is hydrogen or C_1-C_4alkyl; or
the group NR_1R_2 is C_4-C_6alkyleneamino that is unsubstituted or substituted by C_1-C_4alkoxy, hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or by C_1-C_4alkoxycarbonyl, or is morpholino, thiomorpholino or C_1-C_4alkoxycarbonyl-substituted 2,3-dihydro-indol-1-yl;
X is -S- or -NH-; and wherein
the ring A, apart from being substituted by $-SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_4-alkyl, C_1-C_4alkoxy, C_1-C_4alkoxy-C_1-C_4alkoxy, hydroxy, halogen and CF_3; and wherein
the ring B is substituted once or twice by a substituent selected from the group consisting of C_1-C_4alkyl, furyl and pyridyl, and phenyl that is unsubstituted or substituted one or more times by a substituent selected from the group consisting of halogen, C_1-C_4alkoxy, amino, C_1-C_4alkylamino and di-C_1-C_4alkylamino;
or a salt thereof.

The invention relates especially to a compound of formula (I) wherein
X is S and Y and Z are each CH; or
X is NH and Y and Z are each CH; or
X is NH and one of variables Y and Z is N and the other is CH;
R_1 is C_1-C_7alkyl or C_1-C_7alkyl substituted by halogen, C_1-C_7alkoxy, C_1-C_7alkoxycarbonyl, or by C_1-C_7alkylcarbamoyl;
R_2 is hydrogen or C_1-C_7alkyl; or
the group NR_1R_2 is linear C_2-C_6alkyleneamino, pyrrolidino that is unsubstituted or substituted by C_1-C_7alkyl, hydroxy-C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkyl, C_1-C_7alkanesulfonyl-C_1-C_7alkyl, cyano, or by C_1-C_7alkoxycarbonyl, or is morpholino, or C_1-

C_7alkoxycarbonyl-substituted dihydroindol-1-yl or is a group of formula  ; and wherein

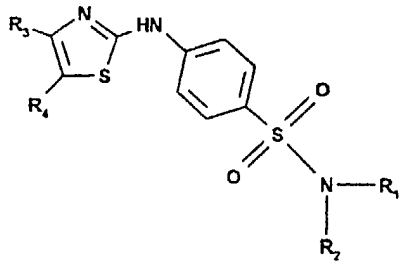
the ring A, apart from being substituted by $-SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, hydroxy, halogen and CF_3; and wherein

R_3 is furyl, thienyl, pyridyl, phenyl, phenyl substituted one or more times by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, and di-C_1-C_7-alkylamino, or is phenyl di-substituted by methyleneoxymethylene; and

R_4 is hydrogen, halogen,C_1-C_7alkyl, C_1-C_7alkoxy, or phenyl;

or a pharmaceutically acceptable salt thereof.

The invention relates especially to a compound of formula (I A)



(I A), wherein

R_1 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkyl-aminocarbonyl-C_1-C_4alkyl; and

R_2 is hydrogen or C_1-C_4alkyl; or

the group NR_1R_2 is pyrrolidino or piperidino, each unsubstituted or substituted by C_1-C_4alkoxy, hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or by C_1-C_4alkoxycarbonyl, or is morpholino, thiomorpholino or C_1-C_4alkoxycarbonyl-substituted 2,3-dihydro-indol-1-yl;

R_3 and R_4 are each independently of the other hydrogen, C_1-C_4alkyl, furyl, pyridyl, or phenyl that is unsubstituted or substituted by halogen, C_1-C_4alkoxy, amino, C_1-C_4alkylamino or by di-C_1-C_4alkylamino;

or a salt thereof.

The invention relates especially to a compound of formula (I A) wherein

R_1 is C_1-C_4alkyl, such as methyl ethyl or n-propyl;

R_2 is hydrogen or C_1-C_4alkyl, such as ethyl; or

the group NR_1R_2 is pyrrolidino that is unsubstituted or substituted, especially in position 2 of the pyrrolidino ring, by hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or C_1-C_4alkanesulfonyl-C_1-C_4alkyl or substituted, especially in position 3 of the pyyrolidino ring, by C_1-C_4alkoxy, such as methoxy;
R_3 is thienyl, pyridyl, phenyl, or phenyl substituted one or more times by a substituent selected from the group consisting of halogen and C_1-C_4alkoxy; and
R_4 is hydrogen, halogen, C_1-C_4alkoxy or phenyl;
or a pharmaceutically acceptable salt thereof.

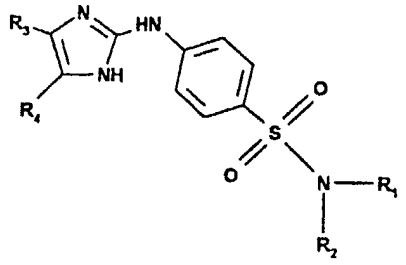
The invention relates especially to a compound of formula (I A) wherein
R_1 is C_1-C_4alkyl, such as methyl; and R_2 is hydrogen or C_1-C_4alkyl, such as methyl; or the group NR_1R_2 is pyrrolidino or piperidino, each unsubstituted or substituted by C_1-C_4alkoxy, hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or by C_1-C_4alkoxycarbonyl; R_3 and R_4 are each independently of the other phenyl that is unsubstituted or substituted by halogen, such as fluorine or chlorine;
or a salt thereof.

The invention relates especially to a compound of formula (I A) wherein R_1 is C_1-C_4alkyl, such as methyl; R_2 is hydrogen; or the group NR_1R_2 is 2-(C_1-C_4alkoxy-C_1-C_4alkyl)-pyrrolidino, such as 2-methoxymethylpyrrolidino; R_3 is phenyl or halo-substituted phenyl, such as 4-chloro- or 4-fluoro-phenyl; and R_4 is hydrogen; or a pharmaceutically acceptable salt thereof.

The invention relates especially to a compound of formula (I A) wherein
the group NR_1R_2 is 2-(C_1-C_2alkoxy-C_1-C_2alkyl)-pyrrolidino, such as 2-methoxymethyl-pyrrolidino; R_3 is phenyl or phenyl substituted in the 4-position by halogen, such as 4-chloro- or 4-fluoro-phenyl; and R_4 is hydrogen;
or a pharmaceutically acceptable salt thereof.

The invention relates especially to a compound of formula (I A) wherein
R_1 is C_1-C_4alkyl, such as methyl; and R_2 is hydrogen; R_3 is phenyl and R_4 is hydrogen;
or a pharmaceutically acceptable salt thereof.

The invention relates especially to a compound of formula (I B)



(I B)

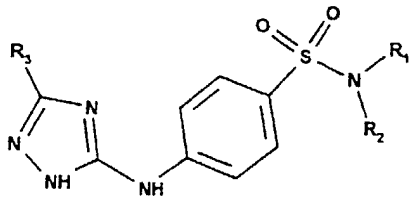
wherein R_1 and R_2, independently of one another, are C_1-C_4alkyl, such as ethyl; or the group NR_1R_2 is 2-(C_1-C_2alkoxy-C_1-C_2alkyl)-pyrrolidino, such as 2-methoxymethyl-pyrrolidino;

R_3 is phenyl; and

R_4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

The invention relates especially to a compound of formula (I C)



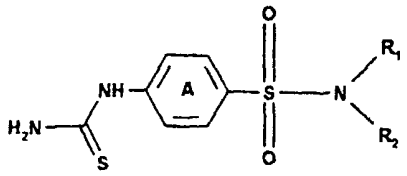
(I C)

wherein the group NR_1R_2 is 2-(C_1-C_2alkoxy-C_1-C_2alkyl)-pyrrolidino, such as 2-methoxy-methylpyrrolidino; and

R_3 is phenyl;

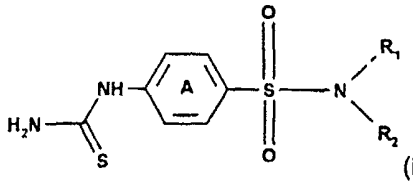
or a pharmaceutically acceptable salt thereof.

The invention relates also to processes for the preparation of the compounds according to the invention. These processes are, for example, as follows: for the preparation of a compound of formula (I) wherein X is -S- and Y and Z are CH, or a compound of formula (I A) or a salt thereof, a compound of formula (II A)


(II A)

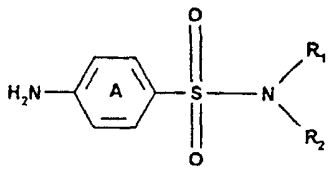
is used as starting material and is reacted in the presence of a base with a compound of formula (R_3)-C=O-C(R_4)-Hal (II B) wherein Hal is halogen, especially bromine.

For the preparation of a compound of formula (I) or (I A) wherein X is -NH- and Y and Z are CH, or a salt thereof, for example a compound of formula (II A)


(II A)

is used as starting material, the thio group is alkylated, for example with a C_1-C_7alkyl iodide, such as methyl iodide, and the resulting compound is then reacted in the presence of a base with a compound of formula (R_3)-CO-C(R_4)-Hal (II B) wherein Hal is halogen, especially bromine.

For the preparation of a compound of formula (I) wherein X is NH and Y is N- and Z is CH, or a salt thereof, there is used as starting material, for example, a hydrazide of formula R_4-CO-NH-NH_2 (II C), which is reacted first with a cyanogen halide, such as cyanogen bromide, and then with a compound of formula (II D)


(II D),

the operations being carried out in the presence of base.

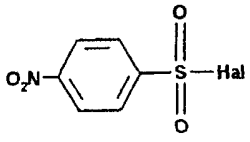
The reactions described hereinabove and hereinbelow are carried out in a manner known *per se*, for example in the absence or, usually, in the presence of a suitable solvent or diluent or a mixture thereof, the operation being carried out as necessary with cooling, at

room temperature or with heating, for example in a temperature range of approximately from -80°C to the boiling temperature of the reaction medium, especially from about -10 ° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

The reaction is preferably carried out in the presence of an organic base. As such a base there come into consideration, for example, a tri-lower alkylamine, such as triethylamine, and also a tri-lower alkylamine having bulky radicals, e.g. ethyldiisopropylamine, or a heterocyclic base, e.g. pyridine, 4-dimethylaminopyridine or N-methylmorpholine.

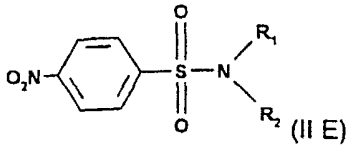
The invention is especially illustrated by the Examples and relates also to the novel compounds mentioned in the Examples and also to their use and to processes for their preparation.

The starting material of formula (II A) can be obtained, for example, by reaction of a compound of formula



(II C),

wherein Hal is halogen, such as chlorine, with a compound of formula H-N(R_1)(R_2) (II D) in the presence of a base, e.g. ethyldiisopropylamine. In the next reaction step, the nitro function in the compound of formula (II E) so obtainable



(II E)

is reduced to the amino group, e.g. by catalytic hydrogenation, for example in the presence of a hydrogenation catalyst, such as Pd/C. By reaction of the compound so obtainable with a suitable isothiocyanate, such as benzoyl isothiocyanate, in the presence of a base, such as sodium carbonate, it is possible to prepare the corresponding thiourea compound of formula (II A).

Salts of compounds of formulae (I) and (I A) can be prepared in a manner known *per se*. For example, acid addition salts of compounds of formulae (I) and (I A) are obtained by treatment with an acid or a suitable ion exchange reagent. Acid addition salts can be converted into the free compounds in customary manner, e.g. by treatment with a suitable basic agent.

Resulting acid addition salts can be converted into other salts in a manner known *per se*, for example by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt formed is insoluble and is therefore eliminated from the reaction equilibrium.

The compounds of formulae (I) and (I A), including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation (solvates).

As a result of the close relationship between the novel compounds in free form and in the form of their salts, hereinabove and hereinbelow any reference to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as appropriate and expedient.

The resulting compound of working example 104 may be used as starting material, e.g. for the manufacture of corresponding acylated or alkylated derivatives thereof. Said compound can also be used for the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidaemia and hypertonia. Furthermore, they could be used in the treatment of loss of memory, epileptic convulsions, migraine, sleep disorders and pain, and additionally in the treatment of sexual disorders, depression, anxiety states, cerebral haemorrhages, shock, decompensated cardiac insufficiency, nasal congestion and diarrhoea. Accordingly, the compound of example 103 and its use is also a subject matter of the present invention.

Resulting mixtures of diastereoisomers and mixtures of racemates can be separated into the pure diastereoisomers and enantiomers in known manner on the basis of the physico-chemical differences between the constituents, for example by means of chromatography and/or fractional crystallisation.

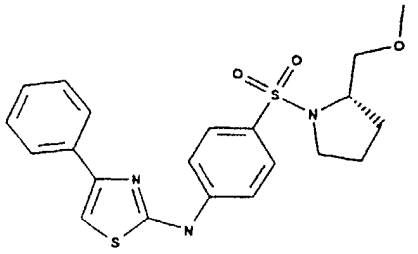
The novel compounds of formula (I) can be used, for example, in the form of pharmaceutical compositions which contain a therapeutically effective amount of the active ingredient, as appropriate together with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers that are suitable for enteral, e.g. oral, or parenteral administration. The pharmaceutical compositions in question, which, if desired, may contain further pharmacologically active substances, are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising procedures, and contain from approximately 0.1% to 100%, especially from approximately 1% to approximately 50%, or in the case of lyophilisates up to approximately 100 %, active ingredient.

The invention relates also to the use of the compounds of formula (I), especially in the preparation of pharmaceutical compositions. The dosage may depend upon various factors, such as the mode of administration, species, age and/or individual condition. The daily doses to be administered are, in the case of oral administration, from about 0.25 to about 10 mg/kg and, for warm-blooded animals having a body weight of about 70 kg, especially from about 20 mg to about 500 mg.

The following Examples serve to illustrate the invention; temperatures are given in degrees Celsius.

Example 1:

[4-(2-Methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(4-phenyl-thiazol-2-yl)-amine



1.52 mmol of [4-(2-methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-thiourea are heated at reflux in 5 ml of ethyl alcohol and 1.52 mmol of triethylamine. 1.52 mmol of phenacyl

bromide are added and the mixture is maintained under reflux for 20 minutes. The reaction mixture is concentrated, taken up in methylene chloride, washed with water and dried over sodium sulfate. After the solvent has been evaporated off using a rotary evaporator, 1.1 equivalents of hydrochloric acid in ethyl alcohol are added. Recrystallisation from ether and drying under a high vacuum at 60 °C yield crystalline [4-(2-methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(4-phenyl-thiazol-2-yl)-amine. M.p. 155 °C.

The starting material can be prepared, for example, as follows:

(a) 2-Methoxymethyl-1-(4-nitro-benzenesulfonyl)-pyrrolidine

22.56 mmol of (S)-2-(methoxymethyl)-pyrrolidine are taken up in 40 ml of methylene chloride, and 22.56 mmol of ethyldiisopropylamine (Hünig base) are added. At 0-10 °C, 22.56 mmol of p-nitrobenzenesulfonyl chloride are then added. The mixture is stirred at room temperature for 2 hours, then washed with water and 2N hydrochloric acid, dried over sodium sulfate and concentrated. Recrystallisation from ether yields 2-methoxymethyl-1-(4-nitro-benzenesulfonyl)-pyrrolidine. Rf value = 0.5 (petroleum ether/ethyl acetate 1:1). Beige crystals.

(b) 2-Methoxymethyl-1-(4-amino-benzenesulfonyl)-pyrrolidine

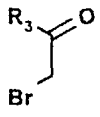
20 mmol of 2-methoxymethyl-1-(4-nitro-benzenesulfonyl)-pyrrolidine are hydrogenated to saturation point in 120 ml of tetrahydrofuran in the presence of 0.6 g of palladium/carbon (10%) at room temperature under normal pressure. The reaction proceeds substantially without secondary products (thin-layer chromatography). The mixture is filtered over Hyflo Super Cel® (kieselguhr, Fluka). Without being further processed the resulting solution in tetrahydrofuran is reacted to form the thiourea in the next step.

(c) [4-(2-Methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-thiourea

20 mmol of benzoyl isothiocyanate are added to 20 mmol of 2-methoxymethyl-1-(4-amino-benzenesulfonyl)-pyrrolidine in 120 ml of tetra hydrofuran (crude product from the hydrogenation of the preceding step). The mixture is stirred at room temperature for 2 hours and then concentrated. 120 ml of methyl alcohol and 20 mmol of potassium carbonate (dissolved in 50 ml of water) are added and the mixture is stirred at room temperature for 4 hours (the reaction mixture becomes a solution) and concentrated. Extraction twice with methylene

chloride, drying over sodium sulfate and concentration by evaporation are carried out, yielding [4-(2-methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-thiourea in the form of a white powder. Rf value = 0.1 (petroleum ether/ethyl acetate 1:1).

2-Bromo-1-phenyl-ethanones of formula



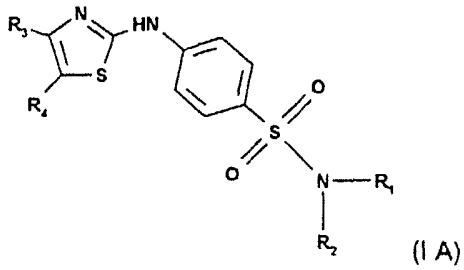
(II F),

wherein R_3 is, for example, phenyl that is unsubstituted or substituted by halogen, C_1-C_7alkoxy, amino, C_1-C_7alkylamino or by di-C_1-C_7alkylamino:

The α-bromoacetophenones that are not commercially available are obtained by treamtent of the corresponding acetophenones with one equivalent of bromine in acetic acid.

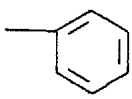
Examples 2-104

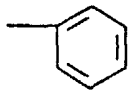
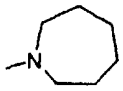
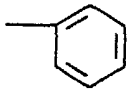
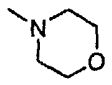
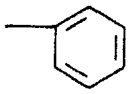
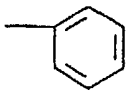
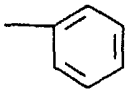
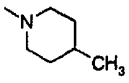
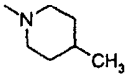
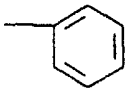
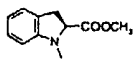
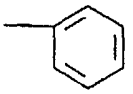
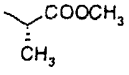
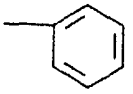
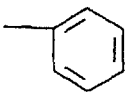
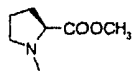
In an analogous manner, e.g. as described in Example 1, it is possible to prepare, for example, the following compounds of formula (I A):

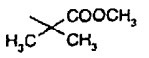
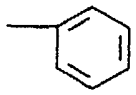
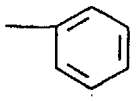
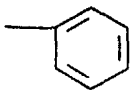
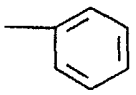
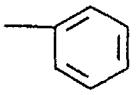
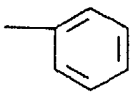
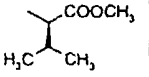
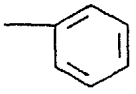
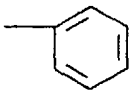
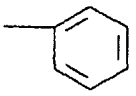
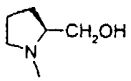


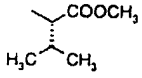
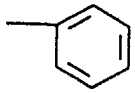
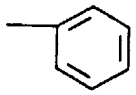
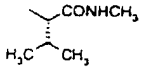
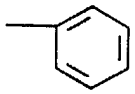
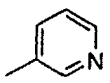
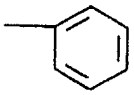
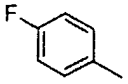
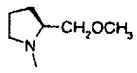
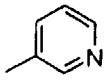
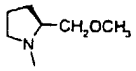
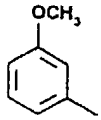
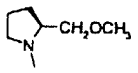
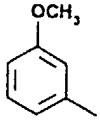
(I A)

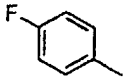
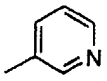
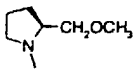
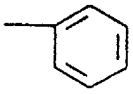
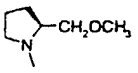
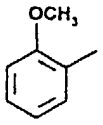
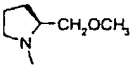
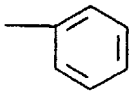
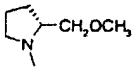
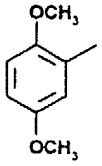
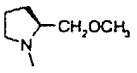
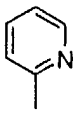
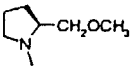
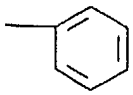
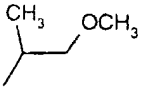
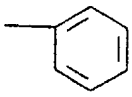
Table 1

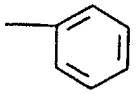
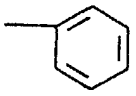
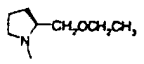
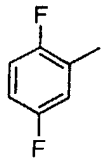
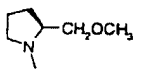
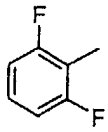
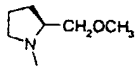
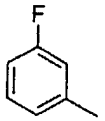
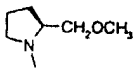
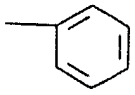
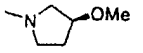
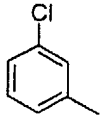
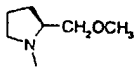
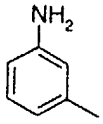
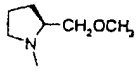
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
2	CH_3	CH_3		H		239

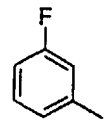
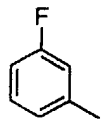
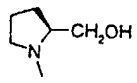
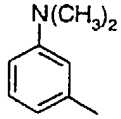
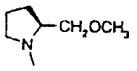
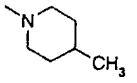
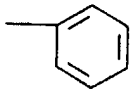
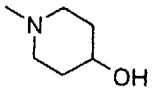
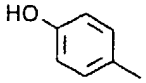
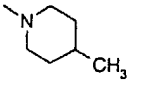
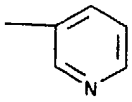
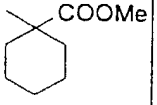
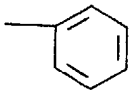
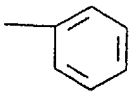
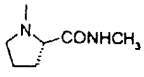
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
3				H		185
4				H		220
5	C_2H_5	C_2H_5		H		143
6	$(CH_3)_2CH$-	H		H		155
7				C_2H_5		180
8				H		170 (HCl)
9				H		188 (HCl)
10	$(CH_3)_2CH$-	C_2H_5		H		183
11		H		H		240 (HCl)
12				H		153

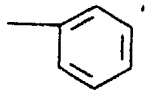
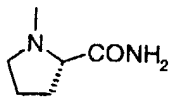
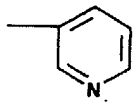
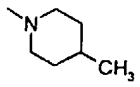
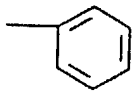
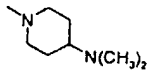
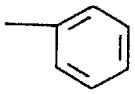
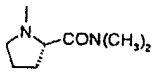
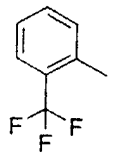
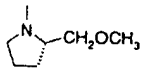
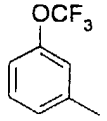
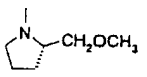
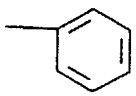
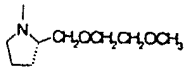
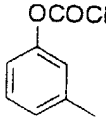
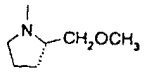
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
13		H		H		180
14	$CH_3OCH_2CH_2$-	H		H		175
15	n-C_4H_9	H		H		172
16	n-C_3H_7	H		H		200
17	C_2H_5	H		H		155
18	tert-C_4H_9	H		H		230
19	n-C_4H_9	H		H		196 (HCl)
20		H		H		183
21	n-C_5H_{11}	H		H		137
22				H		155

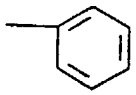
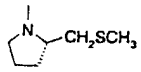
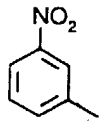
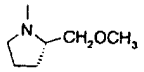
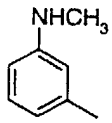
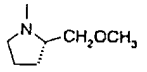
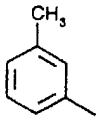
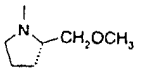
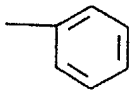
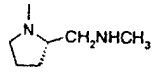
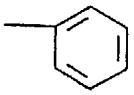
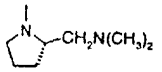
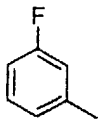
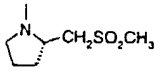
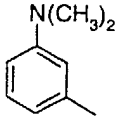
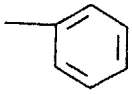
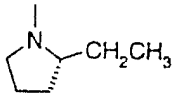
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
23		CH_3		H		157 (HCl)
24	CH_3	H		H		192-194
25		H		H		250
26	CH_3	H				204
27	C_2H_5	C_2H_5		Cl		178
28				H		160 (HCl)
29				H		220
30				H		138 (HCl)
31	CH_3	H		H		148

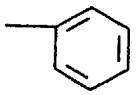
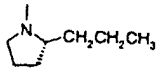
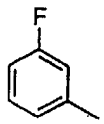
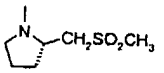
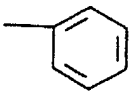
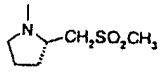
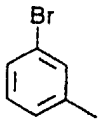
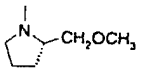
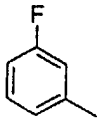
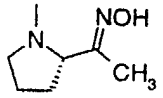
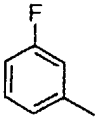
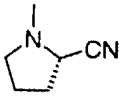
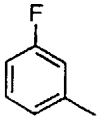
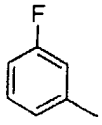
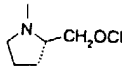
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
32	CH_3	H		H		193
33						225 (HCl)
34				C_2H_5		98
35				H		172 (HCl)
36				H		157 (HCl)
37				H		166 (HCl)
38				H		170
39	$CH_3OCH_2CH_2$	CH_3		H		140 (HCl)
40		H		H		190 (HCl)

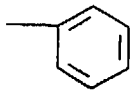
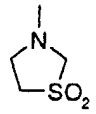
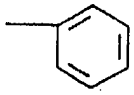
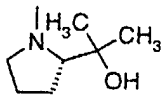
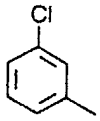
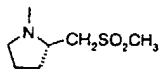
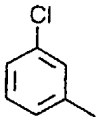
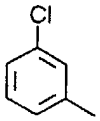
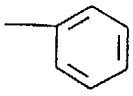
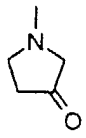
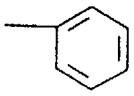
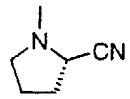
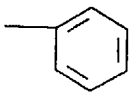
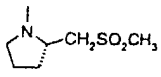
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
41	$CH_3OCH_2CH_2$	C_2H_5		H		156 (HCl)
42				H		147 (HCl)
43				H		120 (HCl)
44				H		166 (HCl)
45				H		155 (HCl)
46				H		150 (HCl)
47				H		150 (HCl)
48				H		amorphous

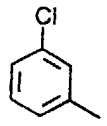
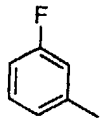
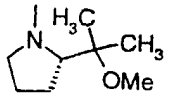
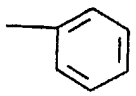
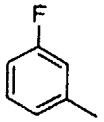
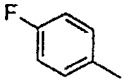
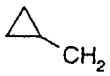
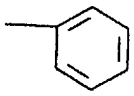
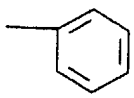
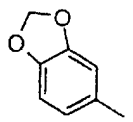
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
49	CH_3	H		H		188
50				H		180 (HCl)
51				H		205
52			H			236
53				H		240
54				H		210
55	CH_2CH_2OH	CH_2CH_2OH				177
56		H		H		188
57				H		152

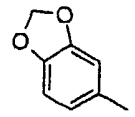
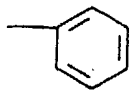
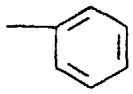
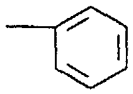
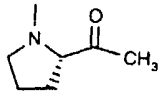
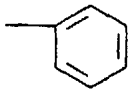
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
58				H		
59						235
60				H		
61				H		140
62				H		130 HCl
63				H		95 HCl
64				H		143
65				H		138 HCl

No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
66				H		133 HCl
67				H		231
68				H		166 HCl
69				H		120 HCl
70				H		
71				H		
72				Cl		245
73	CH_3	H		H		185 HCl
74				H		160 HCl

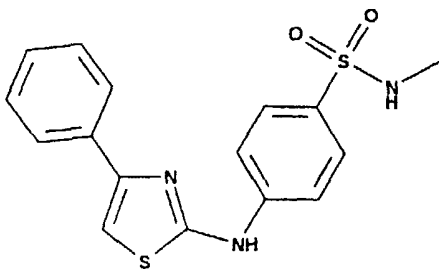
No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
75				H		150 HCl
76				H		195 HCl
77				H		156 HCl
78				H		154 HCl
79				H		255
80				Cl		215 HCl
81	CH_3	H		Cl		180
82				Cl		

No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
83				H		225
84				H		190
85				H		160 HCl
86	CH_3	H		H		135 HCl
87	CH_3	H		Cl		185
88				H		216
89				H		140 CH_3SO_2OH
90				CH_3O		215 CH_3SO_2OH

No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
91	CH_3	H		CH_3		165
92				H		163 CH_3SO_2OH
93	F-CH_2CH_2-	H		H		198 HCl
94	F-CH_2CH_2-	H		H		167 HCl
95	F-CH_2CH_2-	H		H		169 HCl
96		H		H		208 HCl
97 ?	CH_3	H		H		227 HCl
98	CF_3CH_2-	H		H		205 HCl
99	F-CH_2CH_2-	H		H		205 HCl

No.	R_1	R_2	R_3	R_4	NR_1R_2	mp [°C]
100	CF_3CH_2-	H		H		213 HCl
101	CH_3CO	H		H		218 HCl
102	CF_3CH_2-	CH_3		H		163 HCl
103				H		147 HCl
104	H	H		H		247

Example 105: N-Methyl-4-(4-phenyl-thiazol-2-ylamino)-benzenesulfonamide



0.2 mol of N-methyl-4-thioureido-benzenesulfonamide are placed in 300 ml of ethyl alcohol and 0.2 mol of triethylamine. 0.2 mol of phenacyl bromide is added and the mixture is then maintained under reflux for about 60 minutes. The reaction solution is concentrated, taken up in methylene chloride and washed with water. The product already crystallises from the methylene chloride. After evaporation of the solvent using a rotary evaporator,

crystallisation from approximately 600 ml of boiling acetonitrile/water 9:1 is carried out with vigorous stirring. Drying under a high vacuum at 80 °C yields crystalline N-methyl-4-(4-phenyl-thiazol-2-ylamino)-benzenesulfonamide. M.p. 192-194°.

The starting material can be prepared, for example, as follows:

N-Methyl-4-nitro-benzenesulfonamide

0.45 mol of p-nitrobenzenesulfonyl chloride is dissolved in about 2 litres of methylene chloride (about 200 ml of THF can be added). With ice-cooling, about 1 mol (>2 eq.) of methylamine is introduced. More THF can be added if the mixture becomes too thick. Once the pH has become basic, the mixture is stirred at room temperature for about 2 hours to complete the reaction, then washed with water and 2N hydrochloric acid, dried over sodium sulfate and concentrated. Stirring the crystals with ether yields N-methyl-4-nitro-benzene-sulfonamide. Rf value = 0.5 (petroleum ether/ethyl acetate 1:1). Beige crystals.

4-Amino-N-methyl-benzenesulfonamide

0.41 mol of N-methyl-4-nitro-benzenesulfonamide is hydrogenated to saturation point in 1 litre of tetrahydrofuran in the presence of 4.5 g of palladium/carbon (10%) at room temperature for about 1 hour under normal pressure. The mixture is filtered over Hyflo Super Cel® (kieselguhr, Fluka). Without being further processed the resulting solution of 4-amino-N-methyl-benzenesulfonamide in tetrahydrofuran is reacted to form the thiourea in the next step.

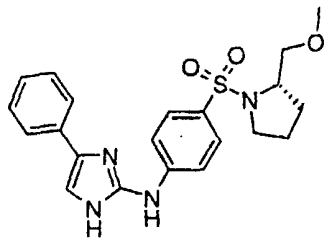
N-Methyl-4-thioureido-benzenesulfonamide

0.41 mol of benzoyl isothiocyanate is added to 0.41 mol of 4-amino-N-methyl-benzene-sulfonamide in 1 litre of tetrahydrofuran (crude product from the hydrogenation of the previous step). The mixture is stirred at room temperature for 2 hours and then concentrated. 1 litre of methyl alcohol and 0.41 mol of potassium carbonate (dissolved in about 300 ml of water) are added to the mixture, which is stirred at room temperature for several hours (until the reaction mixture becomes a solution) and concentrated. Extraction is carried out twice with methylene chloride. Product still present in the water is obtained by salting out the aqueous phase and extracting with tetrahydrofuran and is combined with the methylene chloride phase. Drying over sodium sulfate and concentration by evaporation are

then carried out. Trituration with ether yields N-methyl-4-thioureido-benzenesulfonamide in the form of beige crystals. Rf value = 0.13 (petroleum ether/ethyl acetate 1:1).

Example 106:

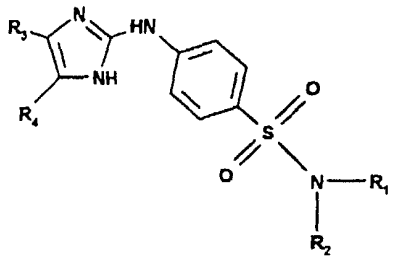
[4-(2-Methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(4-phenyl-1H-imidazol-2-yl)-amine



0.94 ml of methyl iodide is added to 1.0 g of [4-(2-methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-thiourea in 10 ml of ethanol. The mixture is heated at reflux for one hour and then concentrated. The mixture is again taken up in 10 ml of ethanol and, under reflux, 625 mg of 2-amino-1-phenyl-ethanone hydrochloride and 1.14 ml of ethyldiisopropylamine are added. The mixture is maintained under reflux for 3 hours and then, after a further 12, 6, 9 and 35 hours (always reflux), there are additionally added each time 0.3 equivalent of 2-amino-1-phenyl-ethanone hydrochloride and 0.4 equivalent of ethyldiisopropylamine. The mixture is then concentrated, taken up in methylene chloride and washed with water, and the organic phase is dried over sodium sulfate. The crude product is separated by means of flash chromatography (100 g of silica gel 60, eluant petroleum ether/ethyl acetate 3:8). The product is dissolved in a small amount of acetonitrile, and one equivalent of hydrochloric acid in ethanol (8.5N) is added, whereafter [4-(2-methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(4-phenyl-1H-imidazol-2-yl)-amine crystallises overnight at room temperature. Melting point: 193°C.

Example 107:

In an analogous manner, e.g. as described in Example 106, it is possible to prepare, for example, the following compound of formula (I B):

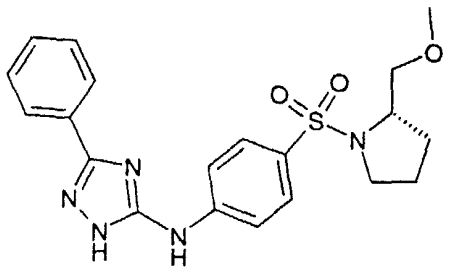


(I B)

Table 2:

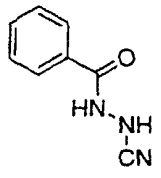
No.	R_1	R_2	R_3	R_4	mp [°C]
108	C_2H_5	C_2H_5		H	245

Example 109:



[4-(2-Methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(5-phenyl-2*H*-[1,2,4]triazol-3-yl)-amine

1.0 g of benzoyl hydrazide, 0.78 g of cyanogen bromide and 1.25 ml of diisopropylethylamine are placed in 15 ml of methylene chloride, and tetrahydrofuran and dioxane are added until a cloudy solution has formed. The solution is stirred at room temperature for 6 hours and then concentrated by evaporation *in vacuo*, and the residue is crystallised from ethanol. The resulting white crystals have the chemical composition of intermediate A:

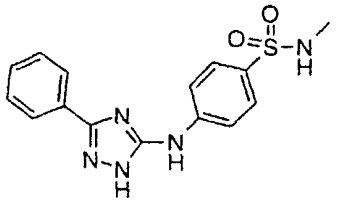


Intermediate A (CAS Reg.No. 62875-15-4)

500 mg of 2-methoxymethyl-1-(4-amino-benzenesulfonyl)-pyrrolidine and 2 ml of dioxane are added to 200 mg of intermediate A. The mixture is heated at reflux for 2.5 hours, cooled and then separated by means of flash chromatography (100 g of silica gel 60, particle size 40-62 micrometers, eluant petroleum ether/ethyl acetate 1:1). [4-(2-Methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(5-phenyl-*2H*-[1,2,4]triazol-3-yl)-amine is obtained. Rf value 0.18 (petroleum ether/ethyl acetate 1:1). Melting point 170-173 °C.

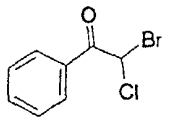
In an analogous manner it is possible to prepare, for example:

N-Methyl-4-(5-phenyl-*2H*-[1,2,4]triazol-3-ylamino)-benzenesulfonamide



Melting point 207°C.

Preparationof starting material:

5-Chlorophenylthiazole derivatives are obtained by treatment of the hydrochloride salts of the corresponding unsubstituted products with meta-chloroperbenzoic acid in methylene chloride (methanol may be added, depending upon the solubility of the reactants) or by reaction of the thiourea with the following compound  .

Example 66:

1 g of the tosylate of {1-[4-(4-phenyl-thiazol-2-ylamino)-benzenesulfonyl]-pyrrolidin-2-yl}-methanol (obtained by treatment of the alcohol with tosyl chloride in pyridine) is placed in 10 ml of N-methylpyrrolidine, and 246 mg of sodium methanethiolate are added. The

mixture is stirred at 50°C for one hour, taken up in ethyl acetate, washed 3 times with water, dried over sodium sulfate, stirred with silica gel and active carbon and filtered over Hyflo. The residue is concentrated by evaporation and then dissolved in acetonitrile; one equivalent of hydrochloric acid in ethanol is added and the resulting crystals are filtered off. [4-(2-Methylsulfanylmethyl-pyrrolidine-1-sulfonyl)-phenyl]-(4-phenyl-thiazol-2-yl)-amine is obtained (hydrochloride) . M.p. 133°C.

Example 72:

About 0.5 ml of methanol and 75 mg of meta-chloroperbenzoic acid are added to 105 mg of [4-(3-fluoro-phenyl)-thiazol-2-yl]-[4-(2-methanesulfonylmethyl-pyrrolidine-1-sulfonyl)-phenyl]-amine (Example 76) in 10 ml of methylene chloride. The reaction mixture is stirred at room temperature for 4 hours, washed with 0.5N aqueous NaOH and once with water, dried and crystallised from ether/ethyl acetate, yielding [5-chloro-4-(3-fluoro-phenyl)-thiazol-2-yl]-[4-(2-methanesulfonylmethyl-pyrrolidine-1-sulfonyl)-phenyl]-amine. M.p. 245 °C.

The starting material for Example 76 can be obtained, for example, as follows:

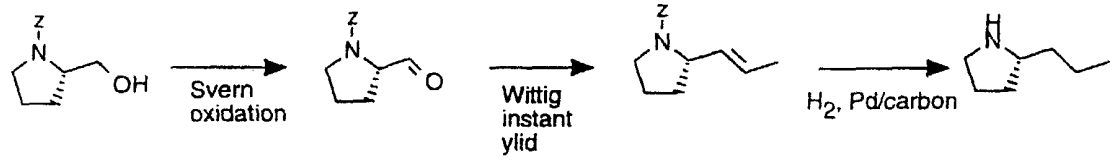
313 mg of meta-chloroperbenzoic acid are added to 250 mg of [4-(3-fluoro-phenyl)-thiazol-2-yl]-[4-(2-methylsulfanylmethyl-pyrrolidine-1-sulfonyl)-phenyl]-amine (manufactured e.g. according to example 1) in 15 ml of methylene chloride and the mixture is stirred at room temperature for one hour. The reaction mixture is washed with 1N aqueous NaOH and water, stirred with active carbon and silica gel and filtered over Hyflo. Drying and crystallisation from HCl/ethanol yield [4-(3-fluoro-phenyl)-thiazol-2-yl]-[4-(2-methanesulfonylmethyl-pyrrolidine-1-sulfonyl)-phenyl]-amine hydrochloride. M.p. 195 °C.

Example 70 or 71, respectively, is obtained by treatment of the tosylate of {1-[4-(4-phenyl-thiazol-2-ylamino)-benzenesulfonyl]-pyrrolidin-2-yl}-methanol (obtained by treatment of the alcohol with tosyl chloride in pyridine) with methylamine and dimethylamine, respectively.

Example 48 is obtained by reduction of the corresponding nitro derivative by means of hydrogenation (10 % Pd/carbon, THF or methanol).

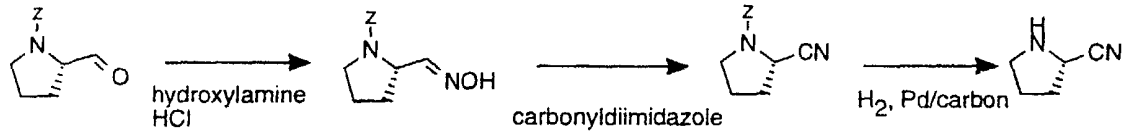
Example 68 is obtained by formylation of the compound of example 48 with the mixed anhydride of formic acid and acetic acid and subsequent reduction with lithium aluminium hydride in tetrahydrofuran.

The amine of the sulfonamide from Example 68 is obtained by Wittig reaction (instant ylid) with the aldehyde of Z-proline and subsequent hydrogenation:



The amine of the sulfonamide from Example 103 is obtained by reaction of the acid chloride of Z-proline with methylmagnesium chloride at –78 °C and subsequent hydrogenation. See Example above.

The amine of the sulfonamide from Example 80 is obtained by treatment of the oxime of the aldehyde of Z-proline with carbonyldiimidazole and subsequent hydrogenation:



Formulation Example: Hard gelatin capsules, comprising 100 mg of active ingredient, e.g. [4-(2-methoxymethyl-pyrrolidine-1-sulfonyl)-phenyl]-(4-phenyl-thiazol-2-yl)-amine or a salt, e.g. the hydrochloride, thereof, can be prepared, for example, as follows:

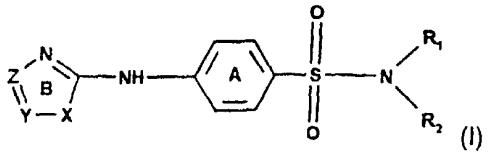
Composition (for 1000 capsules)

active ingredient	100.0 g
lactose	250.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is added through a sieve of 0.2 mm mesh size to the lyophilised active ingredient. The two components are mixed homogeneously together. Then first the lactose is added through a sieve of 0.6 mm mesh size and then the microcrystalline cellulose is added through a sieve of 0.9 mm mesh size. The mixture is then mixed homogeneously again for 10 minutes. Finally the magnesium stearate is added through a sieve of 0.8 mm mesh size. After being mixed for a further 3 minutes, the resulting formulation is introduced in 390 mg portions into size 0 hard gelatin capsules.

What is claimed is:

1. A compound of formula (I)



(I)

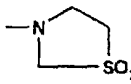
wherein

X is S or NH, and Y and Z are each CH; or

X is NH and one of variables Y and Z is N and the other is CH;

R_1 and R_2, independently of one another, represent hydrogen, C_1-C_7alkyl or C_1-C_7alkyl substituted by hydroxy, halogen, C_1-C_7alkoxy, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, C_3-C_8cycloalkyl or by C_3-C_8cycloalkyl which is substituted by C_1-C_7alkoxy-carbonyl, or represent C_2-C_7-alkanoyl;

whereas at least one of variables R_1 and R_2 is different from hydrogen; or

the group NR_1R_2 is linear C_2-C_6alkyleneamino that is unsubstituted or substituted by C_1-C_7alkyl, hydroxy-C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkoxy-C_1-C_7alkyl, C_1-C_7alkylthio-C_1-C_7alkyl, C_1-C_7alkanesulfinyl-C_1-C_7alkyl, C_1-C_7alkanesulfonyl-C_1-C_7alkyl, amino-C_1-C_7alkyl, C_1-C_7alkylamino-C_1-C_7alkyl, di-C_1-C_7alkylamino-C_1-C_7alkyl, hydroxy, cyano, amino, C_1-C_7alkylamino, di-C_1-C_7alkylamino, C_1-C_7alkanoyl, C_2-C_7hydroxylimino-alkyl, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, or by oxo, or is morpholino, thiomorpholino, 4-C_1-C_7alkylpiperazino, 4-pyridyl-piperazino, tetrahydroquinolin-1-yl, tetrahydroisoquinolin-2-yl, dihydroindol-1-yl or C_1-C_7alkoxycarbonyl-substituted dihydroindol-1-yl or is a group of formula 

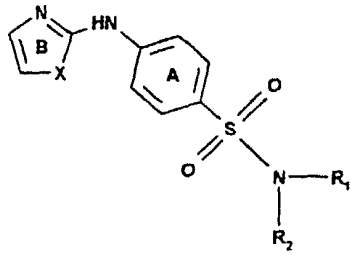
; and

wherein

the ring A, apart from being substituted by $-SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, hydroxy, halogen and CF_3; and wherein the ring B is substituted once or twice via a carbon atom of ring B by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, and phenyl, pyrroyl, furyl, thienyl and pyridyl, each unsubstituted or substituted one or more times by a

substituent selected from the group consisting of hydroxy, halogen, C_1-C_7alkyl, halo-C_1-C_7alkyl, C_1-C_7alkoxy, halo-C_1-C_7alkoxy, C_2-C_7alkanoyloxy, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, di-C_1-C_7alkylcarbamoyl, amino, C_1-C_7alkylamino, di-C_1-C_7alkylamino and N-C_1-C_7alkanoyl-N-C_1-C_7alkylamino, or di-substituted by C_1-C_4alkylene-oxy-C_1-C_4alkylene;
or a salt thereof.

2. A compound according to claim 1 of formula (I')



(I')

wherein
R_1 is C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, carboxy-C_1-C_7alkyl, C_1-C_7alkoxycarbonyl-C_1-C_7alkyl, aminocarbonyl-C_1-C_7alkyl, C_1-C_7alkylaminocarbonyl-C_1-C_7alkyl or di-C_1-C_7alkylamino-carbonyl-C_1-C_7alkyl; and
R_2 is hydrogen or C_1-C_7alkyl; or
the group NR_1R_2 is C_4-C_6alkyleneamino that is unsubstituted or substituted by C_1-C_7alkoxy, hydroxy-C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl or by C_1-C_7alkoxycarbonyl, or is morpholino, thiomorpholino or C_1-C_7alkoxycarbonyl-substituted 2,3-dihydro-indol-1-yl;
X is -S- or -NH-; and wherein
the ring A, apart from being substituted by $-SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, hydroxy, halogen and CF_3; and wherein
the ring B is substituted once or twice by a substituent selected from the group consisting of C_1-C_7alkyl, furyl and pyridyl, and phenyl that is unsubstituted or substituted one or more times by a substituent selected from the group consisting of halogen, C_1-C_7alkoxy, amino, C_1-C_7alkylamino and di-C_1-C_7alkylamino; or a salt thereof.

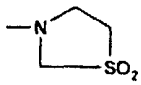
3. A compound according to claim 1 of formula (I) wherein
X is S and Y and Z are each CH; or

X is NH and Y and Z are each CH; or

X is NH and one of variables Y and Z is N and the other is CH;

R_1 is C_1-C_7alkyl or C_1-C_7alkyl substituted by halogen, C_1-C_7alkoxy, C_1-C_7alkoxycarbonyl, or by C_1-C_7alkylcarbamoyl;

R_2 is hydrogen or C_1-C_7alkyl; or

the group NR_1R_2 is linear C_2-C_6alkyleneamino, pyrrolidino that is unsubstituted or substituted by C_1-C_7alkyl, hydroxy-C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkyl, C_1-C_7alkanesulfonyl-C_1-C_7alkyl, cyano, or by C_1-C_7alkoxycarbonyl, or is morpholino, or C_1-C_7alkoxycarbonyl-substituted dihydroindol-1-yl or is a group of formula 

; and wherein

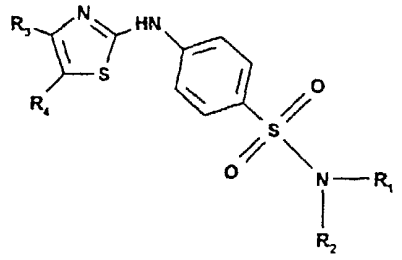
the ring A, apart from being substituted by $-SO_2NR_1R_2$ and -NH-, is unsubstituted or substituted one or more times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, hydroxy, halogen and CF_3; and wherein

R_3 is furyl, thienyl, pyridyl, phenyl, phenyl substituted one or more times by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, and di-C_1-C_7-alkylamino, or is phenyl di-substituted by methyleneoxymethylene; and

R_4 is hydrogen, halogen, C_1-C_7alkyl, C_1-C_7alkoxy, or phenyl;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 of formula (I A)



(I A), wherein

R_1 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkyl-aminocarbonyl-C_1-C_4alkyl; and R_2 is hydrogen or C_1-C_4alkyl; or the group NR_1R_2 is pyrrolidino or piperidino, each unsubstituted or substituted by C_1-C_4alkoxy, hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or by C_1-C_4alkoxycarbonyl, or is morpholino, thiomorpholino or C_1-C_4alkoxycarbonyl-substituted 2,3-dihydro-indol-1-yl; R_3 and R_4 are each independently

of the other hydrogen, C_1-C_4alkyl, furyl, pyridyl, or phenyl that is unsubstituted or substituted by halogen, C_1-C_4alkoxy, amino, C_1-C_4alkylamino or by di-C_1-C_4alkylamino; or a salt thereof.

5. A compound according to claim 4 of formula (I A) wherein

R_1 is C_1-C_4alkyl, such as methyl ethyl or n-propyl;

R_2 is hydrogen or C_1-C_4alkyl, such as ethyl; or

the group NR_1R_2 is pyrrolidino that is unsubstituted or substituted by hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or C_1-C_4alkanesulfonyl-C_1-C_4alkyl or substituted by C_1-C_4alkoxy; R_3 is thienyl, pyridyl, phenyl, or phenyl substituted one or more times by a substituent selected from the group consisting of halogen and C_1-C_4alkoxy; and R_4 is hydrogen, halogen, C_1-C_4alkoxy or phenyl; or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 4 of formula (I A) wherein

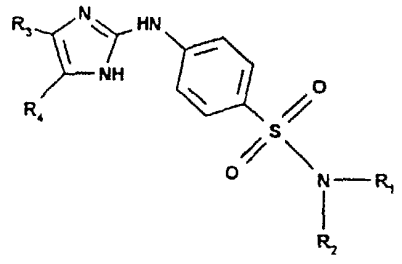
R_1 is C_1-C_4alkyl; and R_2 is hydrogen or C_1-C_4alkyl; or the group NR_1R_2 is pyrrolidino or piperidino, each unsubstituted or substituted by C_1-C_4alkoxy, hydroxy-C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl or by C_1-C_4alkoxycarbonyl; R_3 and R_4 are each independently of the other phenyl that is unsubstituted or substituted by halogen; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 4 of formula (I A) wherein

R_1 is C_1-C_4alky; and R_2 is hydrogen; R_3 is phenyl and R_4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

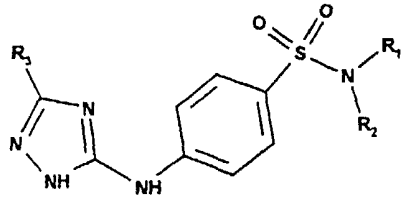
8. A compound according to claim 1 of formula



(I B)

wherein R_1 and R_2, independently of one another, are C_1-C_4alkyl; or the group NR_1R_2 is 2-(C_1-C_2alkoxy-C_1-C_2alkyl)-pyrrolidino; R_3 is phenyl; and R_4 is hydrogen; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 of formula



(I C)

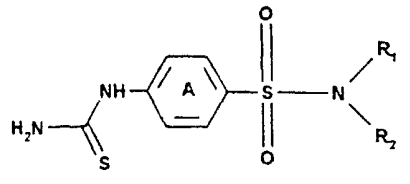
wherein the group NR_1R_2 is 2-(C_1-C_2alkoxy-C_1-C_2alkyl)-pyrrolidino; and R_3 is phenyl; or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of cl aims 1 to 9 for use in the treatment of the human and animal body.

11. The use of a compound of formula (I) or a pharmaceutically acceptable salt of such a compound according to any one of claims 1 to 10 in the preparation of a medicament for the treatment of obesity and related disorders.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable excipient or additive.

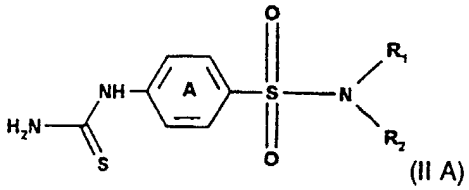
13. A process for the preparation of a compound according to any on e of claims 1 to 9 of a compound of formula (I) or a salt thereof,
(a) wherein X is -S- and Y and Z are CH, comprising using a compound of formula (II A)



(II A)

as starting material, if required alkylating the thio group, and reacting the resulting compound in the presence of a base with a compound of formula (R_3)-C=O-C(R_4)-Hal (II B) wherein Hal is halogen;

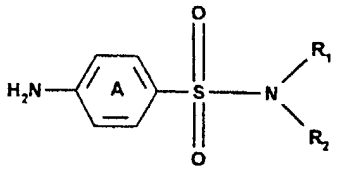
(b) wherein X is -NH- and Y and Z are CH, or a salt thereof, comprising using a compound of formula (II A)



(II A)

as starting material, alkylating the thio group, and reacting the resulting compound in the presence of a base with a compound of formula (R_3)-CO-C(R_4)-Hal (II B) wherein Hal is halogen;

(c) wherein X is NH and Y is N- and Z is CH, or a salt thereof, comprising using as starting material a hydrazide of formula R_4-CO-NH-NH_2 (II C), and reacting first with a cyanogen halide, such as cyanogen bromide, and then with a compound of formula (II D)



(II D),

the operations being carried out in the presence of base.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 98/08333

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/42 C07D417/12 C07D233/88 A61K31/425 C07D249/14
C07D403/12 A61K31/415 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 99, no. 19, 7 November 1983 Columbus, Ohio, US; abstract no. 158309m, J.METRI ET AL: "Synthesis of new sulfamylanilino substituted thiazoles of potential biological activity" page 607; XP002099842 see abstract & EGYPT. J. CHEM., vol. 25, no. 2, 1982, pages 187-189, ---	1,12
A	WO 96 03392 A (G.D.SEARLE & CO) 8 February 1996 see claims --- -/--	1,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 1999	27/04/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/EP 98/08333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 776 765 A (ROTH S) 4 December 1973 see the whole document	1
A	EP 0 614 911 A (SANOFI ELF) 14 September 1994 see page 5, line 22 - line 50; claims	1,10-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 98/08333

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